

Incidence of various clinico-morphological variants of cutaneous tuberculosis and HIV concurrence: a study from the Indian subcontinent

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BACKGROUND AND OBJECTIVES: There are few reports of cutaneous tuberculosis with immunosuppressed states such as HIV, use of immunosuppressants or malignancy. Diagnosis is thus difficult and despite scientific advances such as polymerase chain reaction, it is frequently missed. Although rare, given its worldwide prevalence and the rising incidence of HIV, it is important for clinicians to recognize the variants and promptly treat the patient.

DESIGN AND SETTING: Retrospective study of all cases of cutaneous tuberculosis diagnosed from October 2007 to November 2009 at an outpatient clinic of a tertiary-care hospital in northern India.

METHODS: We collected information on the clinical form of disease, histopathology and HIV concurrence rates and looked for differences in presentation between immunocompetent and immunocompromised states. We also looked for differences and HIV concurrence between immunocompetent and immunocompromised patients. Diagnosis was based on clinical, histopathological and microbiological tests for tuberculosis and a test for HIV.

RESULTS: The overall incidence of cutaneous tuberculosis was 0.7% (131 of 18 720 outpatients). HIV concurrence was 9.1% (12 cases) of all cutaneous tuberculosis cases. Most common variants seen were scrofuloderma (36.5%), lupus vulgaris (31%), tuberculosis verruca cutis (12.9%), lichen scrofulosorum (11.4%), papulonecrotic tuberculids (3.8%), erythema nodosum (2.2%) and erythema induratum of Bazin (1.5%).

CONCLUSIONS: Cutaneous tuberculosis rates were slightly higher in our study than in other studies from India. HIV co-infection rates were similar to those in other studies. Many atypical morphological forms and presentations were observed in HIV co-infected patients. Due to the varied clinical presentations, physician awareness and a high index of suspicion are necessary to diagnose cutaneous forms of tuberculosis.

Robert Koch discovered the causative agent *Mycobacterium tuberculosis* in 1882. Just as with systemic tuberculosis (TB), the cutaneous variants have a variable clinical appearance, significance and prognosis. In India, there were 2.5 million people living with HIV and AIDS at the end of 2007, while the incidence of TB was approximately 1.8 million cases per year.^{1,2} In a survey carried out among new tuberculosis patients under the Revised National TB Control Program in 2007, HIV seroprevalence varied widely and ranged from 1% to 13.8% across 15 districts. Currently, it is unclear what role the HIV epidemic has played in the TB situation in

India. If HIV prevalence in the community continues to rise, however, it could affect the TB control program by decreasing cure rates and increasing mortality and incidence of resistant TB. Furthermore, appropriate management of patients with TB/HIV requires not only treating the TB but referring them for CD4 counts testing and antiretroviral treatment. The continued rise of worldwide pandemic of TB, the rising incidence of HIV-associated TB and less awareness among physicians about diagnosing cutaneous TB due its varied clinical and histopathological picture motivated us to study its features in detail in our region.

METHODS

Our study consisted of a total of 18720 patients who attended the outpatient clinic for skin, venereal diseases and leprosy at Muzaffarnagar Medical College and Teaching Hospital, Uttar Pradesh, India during the period October 2007 to November 2009. On a standard medical record form, demographic details, history, clinical presentations, routine investigations as blood examination, Mantoux test, urine and stool tests, chest X-ray findings; skin biopsy findings, smear for acid-fast bacilli; culture for mycobacteria, fine needle aspiration cytology of lymph nodes, and PCR findings wherever required were recorded. Wherever indicated, further tests were performed to rule out TB in other organ systems of the body. In all the cases in which the diagnosis could still not be confirmed by the above methods, the patients were given antitubercular therapy empirically for 4 weeks, and treatment response was noticed. All the cutaneous TB patients were screened for HIV by the ELISA method.

RESULTS

Of the 18 720 outpatients seen during the 2-year period, cutaneous TB was confirmed in 131 (0.7%) patients. Prevalence of HIV infection among all the patients attending our institute was found to be 0.16%. There were a total of 4357 patients with various forms of TB receiving care at our hospital during the 2-year period. The ratio of the incidence of cutaneous TB to that of all forms TB was found to be 3.0%. Apart from orificial TB, all variants of cutaneous TB were seen in our study (Table 1).

The most commonly seen variant was scrofuloderma (48 cases). Most cases had a single site involved, but 6 cases (12.5% of all scrofuloderma cases) had multiple sites involved. Most patients were of low socioeconomic status. The most common underlying structure involved was lymph nodes in 39 cases (81.2% of all scrofuloderma cases), followed by bony structures in 8 cases (16.6% of all scrofuloderma cases). One case of direct extension from epididymis was found (2% of all cases). Scrofuloderma was predominantly seen in younger subjects (mean age, 23.4 years) as compared to other variants. Pulmonary TB was present in 40% of cases (19 patients). Five cases (10.4% of all scrofuloderma cases) were HIV positive. Some common observations with HIV co-infection were extensive contiguous lymph node sites (Figure 1), simultaneous involvement of more than one underlying structure, such as lymph nodes and bones (Figure 2), and involvement of pulmonary TB was more common.

The second most commonly seen variant was lupus

vulgaris (40 cases). The most common form was the typical asymptomatic plaque form. One case of lupus hypertrophicus of the pinna was found (Figure 3). Associated pulmonary TB was found in 12 cases (30% of all lupus cases). Cervical lymphadenitis was present in 14 cases (35% of all lupus cases), and 2 cases showed post-BCG vaccination TB (5% of all cases of lupus). The Mantoux test revealed >10 mm induration in 31 cases (77.5% of all lupus cases), with 25 cases showing positivity with >15 mm induration values. Three cases (7.5% of all lupus cases) were HIV positive and included two adults and one child of 14 years. Thirteen cases showed a single plaque-like lesion; in three cases, more than one lesion was present. Of the 3 HIV-positive cases, one case had more than one plaque lesion present (Figure 4); two cases were associated with systemic lesions (one case showed pulmonary TB, and one case showed associated cervical lymphadenitis); and single-plaque lesions were more extensive and widespread in distribution.

Tuberculosis verruca cutis (TVC) was found in 17 cases. The mean age at presentation was also, low (27.2 years) compared to other variants. It was most commonly seen on exposed sites, with the extremities being the most commonly involved, followed by the face. Two cases (11.7%) were HIV positive. Mantoux tests were highly positive in all cases except the two HIV posi-

Table 1. Types of cutaneous tuberculosis and presence of pulmonary tuberculosis and HIV positivity.

	Type of cutaneous tuberculosis	Pulmonary tuberculosis	HIV positive
Scrofuloderma	48 (36.6)	19	5
Lupus vulgaris	40 (30.5)	12	3
Tuberculosis verruca cutis	17 (12.9)	0	2
Lichen scrofulosorum	11 (8.4)	0	0
Papulonecrotic tuberculids	5 (3.8)	0	0
Erythema nodosum	3 (2.5)	0	0
Erythema induratum of Bazin	2 (1.5)	0	0
Primary inoculation tuberculosis	1 (0.8)	0	0
Tubercular cellulitis	1 (0.8)	0	1
Metastatic tubercular abscess	1 (0.8)	0	1
Acute miliary tuberculosis	1 (0.8)	0	0
BCG inoculation tuberculosis	1 (0.8)	0	0
Total	131		12

Values are n (%).



Figure 1. Scrofuloderma in an HIV-positive child showing multiple undermined ulcers, pus and discharging sinuses in the neck, axillary, pre-sternal and chest regions with puckered scar marks in the axillary region.



Figure 2. Scrofuloderma in an HIV-positive child showing involvement of the sub-mental lymph nodes, ribs and forearm bones. Additionally, small, bluish, papular lesions are visible and show dissemination.

tive patients. Both the HIV-positive patients presented with more than one hyperkeratotic lesions (**Figure 5**).

Lichen scrofulosorum was seen in 11 cases (8.3% of total cases). The tuberculin test was strongly positive in all cases. Interestingly, none of the cases was HIV positive. Five cases (3.8% of total cases) had papulonecrotic tuberculids (**Figure 6**), three (2.2% of total cases) had erythema nodosum (confirmed by histology and PCR), and two had erythema induratum of Bazin (1.5% of total cases) (**Figure 7**). These were confirmed by histopathological examination (**Figure 8**) and PCR of tissues. Both patients were of medium build, with no erythrocytotic changes, contrary to reports in the literature. Additionally, there was one case each of primary inoculation TB, tubercular cellulitis, metastatic tubercular abscess, acute miliary TB and BCG inoculation TB. Patients were HIV positive in 2 cases (one with tubercular cellulitis and one with metastatic tubercular abscess).

In 96 patients (73.3% of cutaneous TB cases), the erythrocyte sedimentation rate was elevated (>30 in the first hour by the Westergren method), while anemia (<10.0 g hemoglobin) was present in 55 cases (42%). Of the 131 patients, only 17 were BCG vaccinated, with the remaining 114 being unvaccinated. Histopathologies of 68 patients were positive and most of those were consistent with either epithelioid granulomas, necrosis, giant cells, pseudoepitheliomatous hyperplasia, chronic inflammatory cell infiltrate, or granulomatous vasculitis with 27 patients showing a nonspecific inflammatory infiltrate. Acid-fast bacilli (AFB) were demonstrable in only two cases of sputum smear examination. Lesional fine needle aspiration cytology of all cases with metastatic tubercular abscess and four cases of scrofuloderma showed positive AFB smears. There was no difference in histology between HIV-positive and HIV-negative cases. Urine sediment of the two patients with erythema induratum of Bazin showed positive AFB culture. X-ray of the chest showed lung involvement in 31 patients and hilar adenopathy in 22 patients. HIV was reactive by the ELISA method in 12 patients (9.1% of all cutaneous TB cases).

Treatment was given to all patients by short-course directly observed therapy, under which 12 (9.1%) patients were lost to follow-up, 3 (2.2%) died (2 were concomitantly HIV positive and 1 had miliary TB). One hundred sixteen patients were given a standard regimen of 4 drugs (rifampicin, isoniazid, ethambutol and pyrazinamide) for a duration of 6 to 9 months. In 9 (18.7% of all scrofuloderma patients), 5 (12.5% of all lupus vulgaris patients) and 7 (41.1% of all TB ver-



Figure 3. Lupus hypertrophicus of the pinna showing an extensive, soft, reddish yellow hypertrophic plaque with absent scaling or scarring. The lesion had been present for the previous 25 years.



Figure 4. Lupus vulgaris in an HIV-positive case with multiple typical plaque lesions showing peripheral extension and central atrophy.



Figure 5. Tuberculosis verruca cutis showing verrucous hyperkeratotic warty lesions on the feet.



Figure 6. Papulonecrotic tuberculids on the chest region showing necrotizing papules.

ruca cutis patients) patients, additional plastic reconstructive surgery along with multidrug therapy were used to reduce morbidity. Additionally, 6 patients were given various drugs such as minocycline, amikacin, and streptomycin along with multidrug therapy for variable durations with good results.

DISCUSSION

The incidence of both pulmonary and extrapulmonary TB is expected to rise. The emergence of HIV virus has led to a 20% increase in incidence of extrapulmonary TB in the U.S.³ Various other factors implicated in the rising incidence of TB could be ease of migration of people across the globe, the rise in immunosuppressive therapy, the decline in TB-control efforts and the emergence of resistant strains of *M tuberculosis*.



Figure 7. Erythema induratum of Bazin showing extensive ulceration, bridging fibrosis and healing with scarring.

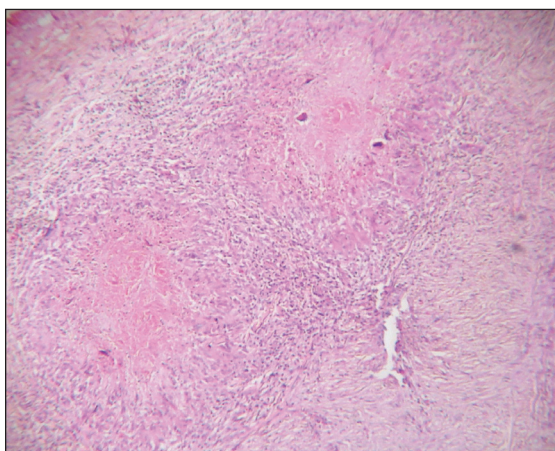


Figure 8. Erythema induratum of Bazin. Necrotizing vasculitis with granuloma (Hematoxylin and eosin stain, ×400)

The overall prevalence of cutaneous TB in our study (0.7%) was a little higher than that found in other Indian studies, which have reported a prevalence of 0.59%, by Singh,⁴ 0.50% by Banerjee,⁵ 0.28% by Pandhi et al,⁶ 0.24% by Satyanarayan,⁷ and 0.26% by Patra et al.⁸ The strains of TB are unknown since culture was not done to determine the strain. Scrofuloderma was the commonest presentation in our study. Sehgal et al,⁹ also from Delhi, found it to be the commonest variant. Scrofuloderma represents direct extension into the skin from an underlying tubercular focus, most commonly tubercular lymphadenitis or skeletal TB. Cervical lymph nodes are most commonly involved. Scrofuloderma presents relatively early due to higher visibility, more symptoms and the greater number of cases of tubercular lymphadenopathy associated with it. Additionally, consumption of unboiled/unpasteurized milk leading to infection by *M bovis*, in turn, leading to cervical node infection via tonsils, may be one factor in India leading to higher scrofuloderma prevalence rates. In Uttar Pradesh, the preponderance of cattle rearing and subsequent practice of unboiled milk consumption may be a factor contributing to high scrofuloderma prevalence rates. Mean age groups of presentation was lower (23.4 years) as compared to other age groups.

The next most common variant (lupus vulgaris) is a cutaneous post-primary TB occurring in previously sensitized individuals who have a high degree of tuberculin sensitivity, although immunity is low to moderate. In contrast to Western countries, where it is found commonly on the face, in India and other developing nations, it commonly involves the extremities and the buttocks. Lesions occur in normal skin after direct extension from underlying tubercular focus, by lymphatic or hematogeneous spread, after primary inoculation, after BCG vaccination or in old scrofuloderma scars.¹⁰ Rarely, it may occur after re-infection of the skin in persons with high degree of tuberculin sensitivity.¹¹ Kumar et al,¹⁰ Patra et al,⁸ and Ho et al¹² found lupus vulgaris to be the commonest variant in their studies (55%, 57.69%, and 4% of patients, respectively). One case of an unusual variant of lupus hypertrophicus of the pinna was found.

TVC was encountered in 17 (12.9%) cases, most commonly as exposed sites. It is an exogenous cutaneous infection in a host with moderate-to-high tuberculin sensitivity and usually presents as hyperkeratotic (verrucous) lesions on exposed sites, mostly on the extremities and face. Padmavathy et al¹³ have reported an incidence of TVC of 27.3% in their study. Similarly Patra et al⁸ (19.23%), Archarya et al¹⁴ (32%) reported

variable incidences of TVC in their studies. Erythema induratum was seen in two patients, both females. It mainly affected the legs, which is in accordance with other reports. Of the three patients with erythema nodosum, all had evidence of TB elsewhere in the body.

We encountered 12 cases (9.1%) in our study that were found to be reactive to HIV by the ELISA method. They were confirmed by rapid tests. Viswanathan et al,¹⁵ reported a similar incidence of 13.7% in their study, which was similar to that reported by Quiros et al (20%).¹⁶ While TB prevalence has remained stable, the incidence continues to rise, especially in developing countries. HIV being the most important known risk factor that promotes progression to active TB in people with *M tuberculosis* infection, the number of cases of both pulmonary and extrapulmonary TB is expected to rise. In India and sub-Saharan Africa, TB is the commonest opportunistic infection, and 50% to 60% of AIDS patients have had TB during the course of their illness.¹⁷ Despite isolated case reports of the coexistence cutaneous TB and HIV, we found few studies of such cases in the literature. Although the number of such cases was small and no statistical correlation could be observed, we have tried to bring attention to the importance of such lesions in diagnosing underlying immunosuppressed states and for the appropriate management of such patients. In all cases of true cutaneous TB, there was a good response to anti-TB treatment, this being a good sign since multidrug resistance is being observed now. Unlike pulmonary TB, there are no definite guidelines for treatment of multidrug-resistant cutaneous TB.

In conclusion, cutaneous TB remains one of the least studied and reported variants of TB. The diagnosis in a country like India still relies on tests like

the Mantoux, the chest X-ray, histopathology, and sputum smear examination, none of which is absolute in terms of diagnosis. Polymerase chain reaction is a rapid method of diagnosis but requires expertise, as it is prone to contamination and false positives. Tissue culture remains the gold standard for diagnosis and for monitoring the emergence of drug-resistant strains, but it is time consuming. We found certain lesions that if present, though not always positive, should raise doubts of coexistence of HIV infection:

- Extensive widespread lesions, either single or multiple.
- Involvement of more than one contiguous or noncontiguous site.
- Involvement of more than one underlying structure, for example, lymph nodes and bones.
- Unusual site involvement, for example, epididymis or pinna.
- Miliary TB, or metastatic tubercular abscess.

The global impact of the converging dual epidemics of TB and HIV is one of the major health challenges of our times. Since extrapulmonary, disseminated and sputum smear-negative manifestations are more common in patients with advanced immunosuppression, newer diagnostic tests, which are not only sensitive and specific but also easy to use in remote settings and are cost effective, are required for dealing with this emerging epidemic. Meanwhile, physician awareness in terms of varied presentations and strong clinical suspicion is a must in diagnosing these diseases. We thus conclude that in all patients with cutaneous TB, HIV testing should be done routinely to rule out concomitant HIV and TB.

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